



THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

# Human Parvovirus 4 Infection among Mothers and Children in South Africa

**Citation for published version:**

Matthews, PC, Sharp, CP, Malik, A, Gregory, WF, Adland, E, Jooste, P, Goulder, PJR, Simmonds, P & Klenerman, P 2015, 'Human Parvovirus 4 Infection among Mothers and Children in South Africa', *Emerging Infectious Diseases*, vol. 21, no. 4, pp. 713-715. <https://doi.org/10.3201/eid2104.141545>

**Digital Object Identifier (DOI):**

[10.3201/eid2104.141545](https://doi.org/10.3201/eid2104.141545)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Publisher's PDF, also known as Version of record

**Published In:**

Emerging Infectious Diseases

**Publisher Rights Statement:**

Article in the public domain and free to use.

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



affected during this epidemic. Fourteen patients died; these deaths occurred in Kathmandu, the capital of Nepal, or in different cities in India after these patients were transferred there for better treatment. Fifty pregnant women had acute jaundice, but none of these women died.

The epidemic was presumed to be caused by consumption of contaminated water (3). In February and March 2014, water and sewerage pipelines were damaged in different areas of Biratnagar during construction and repair of roads. A survey conducted by the Department of Community Medicine, B.P. Koirala Institute of Health (Dharan, Nepal), found high levels of coliform bacteria in water supplies from different areas in Biratnagar during the epidemic. Tap water also looked cloudy and visibly contaminated (3).

To obtain more information about the epidemic, the incidence of acute jaundice was determined for 656 prisoners and 75 security personnel at the Biratnagar Jail. The study protocol was approved by the Liver Foundation Nepal. Informed consent was not obtained because identity of patient samples remained anonymous. Acute jaundice was detected among 30 (4.6%) prisoners and 4 (5.3%) security personnel. The same source of consumable water was used by the general population, inmates, and security personnel in Biratnagar.

To identify the causative agent of this epidemic, serum samples from 48 patients were obtained at Koshi Zonal Hospital, the largest government hospital in this zone. Hepatitis A virus RNA and IgM against hepatitis B virus core antigen was not detected in the 48 serum samples. Conversely, IgG, IgM, and IgA against HEV were detected in 47 (97.9%), 45 (94%), and 45 (94%) serum samples, respectively, and HEV RNA was detected in 42 (87.5%) of 48 serum samples, which indicated that the epidemic was caused by HEV.

A partial 412-nt sequence from open reading frame 2 corresponding to nt 5944–6355 of the HEV B1 genome (4) was obtained as reported (5). We obtained 40 HEV isolates from the 42 samples and sequenced partial 412-nt segments. All 40 HEV sequences from the epidemic in Biratnagar segregated into a cluster within genotype 1a (Figure). These sequences showed 99.8% nt identity with each other but only 90.8%–95.4% nt identity with other HEV isolates from Nepal and those from India, Bangladesh, Pakistan, and China.

Compared with previous HEV epidemics in Nepal (6) and other parts of the Indian subcontinent, the local government of Biratnagar and central government of Nepal took steps to contain the reported epidemic. Activities of public and private sectors in Biratnagar ended the epidemic in ≈12 weeks, and no new cases of acute jaundice have been reported in Biratnagar.

Persons in Biratnagar were given information regarding epidemics and ways to contain them. They were

instructed by electronic media to use boiled water for consumption. It became clear that additional information regarding about maintaining water and sewerage systems during road construction and repair should also be provided. Because 14 patients died of HEV infection during this epidemic, more preparedness for epidemics of waterborne diseases is required to minimize unnecessary illnesses and deaths.

## References

1. Kantipur E. com. Jaundice outbreak: Biratnagar schools shut for 5 days [cited 2014 May 12]. <http://www.ekantipur.com/2014/05/12/top-story/jaundice-outbreak-biratnagar-schools-shut-for-5-days/389469.html>
2. Ghimeri B. Alert issued against jaundice in Biratnagar [cited 2014 Apr 30]. <http://www.ekantipur.com/2014/04/30/national/alert-issued-against-jaundice-in-biratnagar/388967.html>
3. Gautam M. Jaundice outbreak: experts blame contaminated water [cited 2014 May 12]. <http://www.ekantipur.com/2014/05/12/top-story/jaundice-outbreak-experts-blame-contaminated-water/389436.html>
4. Tam AW, Smith MM, Guerra ME, Huang CC, Bradley DW, Fry KE, et al. Hepatitis E virus (HEV): molecular cloning and sequencing of the full-length viral genome. *Virology*. 1991; 185:120–31. [http://dx.doi.org/10.1016/0042-6822\(91\)90760-9](http://dx.doi.org/10.1016/0042-6822(91)90760-9)
5. Takahashi K, Okamoto H, Abe N, Kawakami M, Matsuda H, Mochida S, et al. Virulent strain of hepatitis E virus genotype 3, Japan. *Emerg Infect Dis*. 2009;15:704–9. <http://dx.doi.org/10.3201/eid1505.081100>
6. Shrestha SM. Hepatitis E in Nepal. *Kathmandu Univ Med J (KUMJ)*. 2006;4:530–44.

Address for correspondence: Sheikh M.F. Akbar, Department of Medical Sciences, Toshiba General Hospital, 6-3-22 Higashi Oi, Shinagawa-Ku, Tokyo 140-8522, Japan; email: [sheikh.akbar@po.toshiba.co.jp](mailto:sheikh.akbar@po.toshiba.co.jp)

## Human Parvovirus 4 Infection among Mothers and Children in South Africa

**Philippa C. Matthews, Colin P. Sharp, Amna Malik, William F. Gregory, Emily Adland, Pieter Jooste, Philip J. R. Goulder, Peter Simmonds, Paul Klennerman**

Author affiliations: University of Oxford, Oxford, UK (P.C. Matthews, A. Malik, E. Adland, P.J.R. Goulder, P. Klennerman); Oxford University Hospitals, Oxford (P.C. Matthews, P. Klennerman); The University of Edinburgh, Midlothian, Scotland, UK (C.P. Sharp, W.F. Gregory, P. Simmonds); University of Free State, Kimberley, South Africa (P. Jooste); NIHR Biomedical Research Centre, Oxford (P. Klennerman)

DOI: <http://dx.doi.org/10.3201/eid2104.141545>

**To the Editor:** Human parvovirus 4 (PARV4) is a single-stranded DNA virus in the family *Parvoviridae* (1).

In Western countries, IgG against PARV4 is largely found only in persons with risk factors for parenteral infection and is strongly associated with co-infection with bloodborne viruses (2–4). In Africa, transmission seems to be more complicated; reported PARV4 seroprevalence is 4%–37%, even among persons at low risk and with no evidence of HIV or hepatitis C virus (HCV) co-infection (1,5,6).

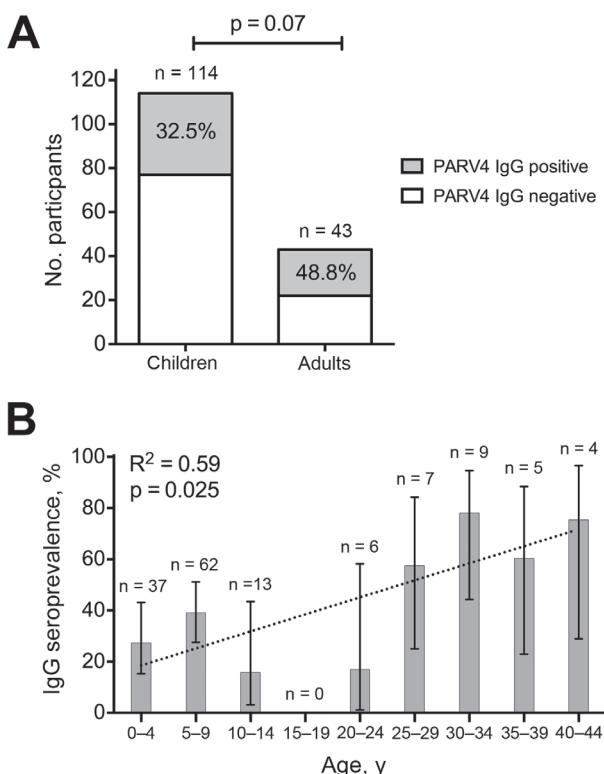
The clinical significance of PARV4 infection remains uncertain. Infections may be asymptomatic, but a variety of clinical associations have been reported (1,7), including an increased rate of progression to AIDS in persons co-infected with HIV (8). This association raises particular concerns for many African populations in which these viruses are co-endemic.

To characterize the epidemiology of PARV4 infection in South Africa, we studied adults and children from pediatric outpatient clinics in Kimberley, South Africa, during May 2009–August 2013. Of the 157 participants, 90 were HIV-1–infected children, 24 their HIV-negative siblings, and 43 HIV-1–infected mothers (of whom 4 had >1 child enrolled). Approval was given by the Ethics Committee of the Faculty of Health Science, University of Free State, South Africa. Written consent was given by all adults and parents/guardians on behalf of their children.

Blood samples were collected from participants, and serum was tested for evidence of PARV4 infection by using ELISA (in duplicate) to detect IgG against PARV4 viral protein 2 (3,6) and by using PCR to detect PARV4 DNA (9). For 92 patients, HIV RNA loads were available; testing was performed by using the Abbott Laboratories m2000 platform (Abbott Park, IL, USA). For 118 of the HIV-infected patients, CD4<sup>+</sup> T-cell counts were ascertained by flow cytometry. Statistical analyses were undertaken by using Prism version 6.0f and online software (<http://graphpad.com/quickcalcs/>). Confidence intervals were calculated by using the adjusted Wald method (<http://www.measuringusability.com/wald.htm>).

We detected IgG against PARV4 in 58 (37%) of 157 patients; this proportion is broadly comparable with that reported from other settings in sub-Saharan Africa, including Burkina Faso, the Democratic Republic of the Congo, and a previous cohort of HIV-infected persons in South Africa (5). Although routes of transmission in Africa remain to be characterized, these high seroprevalence rates support the possibility that some PARV4 transmission may be occurring by nonparenteral routes, as suggested by others (5,10).

PARV4 IgG seroprevalence was higher among adults (49%) than children (33%), although this difference did not reach statistical significance ( $p = 0.07$ , Fisher exact test; Figure, panel A). We found a significant relationship between increasing age and PARV4 IgG serostatus ( $R^2 = 0.59$  by linear regression,  $p = 0.025$ ; Figure, panel B). The numbers in each group are small, and further work is needed to



**Figure.** Relationship between age and seroprevalence of IgG against human parvovirus 4 (PARV4) among 157 mothers and children in Kimberley, South Africa, 2009–2013. A) Number and proportion of children and adults seropositive for IgG against PARV4; the number in each group is shown above the bar.  $p$  value calculated by using the Fisher exact test. B) Proportion of population seropositive for IgG against PARV4 according to age; the number in each group is shown above the bar. Data are shown for 143 persons because no date of birth was recorded for 2 children and 12 adults. Error bars show 95% CIs calculated by the adjusted Wald method.  $R^2$  was calculated by linear regression (dotted line). We considered whether maternal antibodies might be contributing to PARV4 IgG seroprevalence among those 0–4 years of age. However, from 11 children in this group who were  $\leq 12$  months of age (in whom detection of maternal antibody might still be expected), 2 were PARV4 IgG seropositive, and only 1 of these had an IgG-positive mother, suggesting that maternal antibodies did not contribute significantly to PARV4 seropositivity in this cohort.

define this association with more confidence. We did not detect any cases of PARV4 viremia, suggesting that chronic viremia or reactivation are probably uncommon, even among HIV-infected patients.

On the basis of previously reported data demonstrating PARV4 viremia in neonates (7), we hypothesized that vertical transmission is possible. To investigate further, we sought evidence of concordance between IgG serostatus of mothers and their children. Maternal PARV4 IgG status did not differ between IgG-positive and IgG-negative children ( $p = 1.00$ , Fisher exact test; online Technical Appendix Table 1,

<http://wwwnc.cdc.gov/EID/article/21/4/14-1545-Techapp1.pdf>). The absence of correlation between the IgG statuses of mothers and children suggests that vertical transmission is probably not a major contributor to new infections, although it remains plausible that it may sometimes occur.

Data from Europe that suggest an association between PARV4 infection and progression to Centers for Disease Control and Prevention B-syndromes in HIV-positive persons are problematic because of confounding high rates of HCV infection and injection drug use in the PARV4-positive group (8). We sought evidence for this effect in our cohort, in which rates of HCV infection and injection drug use were likely to be negligible. We found no evidence of a PARV4 serostatus effect on HIV RNA load or CD4+ T cells in children ( $p = 0.13$ ,  $p = 0.68$ , respectively; online Technical Appendix Table 1) or adults ( $p = 0.15$ ,  $p = 0.77$ , respectively; online Technical Appendix Table 2).

We found an unexpected negative correlation between PARV4 IgG and HIV status in children ( $p = 0.05$ , Fisher exact test; online Technical Appendix Table 1). One possible explanation is that a detectable PARV4 IgG response is not mounted or maintained in the context of HIV infection; however, this theory is not supported by previous studies in which PARV4 IgG seems to be more prevalent in HIV-infected populations (5,8).

Our analysis was limited by small numbers tested and the retrospective approach to sample testing. Demographic data were not recorded for this cohort, so we are unable to explore further possible social or demographic risk factors that might correlate with PARV4 infection.

This study contributes to an evolving body of data suggesting that PARV4 is highly endemic to different settings across Africa. The unknown clinical effects and transmission routes of this virus remain pressing questions for future research.

P.C.M. is a National Institute for Health Research Clinical Lecturer and received funding from Oxford University Clinical Academic Graduate School and the John Fell Fund to cover the cost of this work. C.P.S., W.F.G., and P.S. were funded by the Biotechnology and Biological Sciences Research Council. P.J.R.G. is a Wellcome Trust Senior Investigator. P.K. is funded by the National Institute for Health Research Biomedical Research Centre, Oxford Martin Centre, and Wellcome Trust grant no. 091663.

## References

1. Matthews PC, Malik A, Simmons R, Sharp C, Simmonds P, Klennerman P. PARV4: an emerging tetraparvovirus. *PLoS Pathog*. 2014;10:e1004036. <http://dx.doi.org/10.1371/journal.ppat.1004036>
2. Sharp CP, Lail A, Donfield S, Gomperts ED, Simmonds P. Virologic and clinical features of primary infection with human parvovirus 4 in subjects with hemophilia: frequent transmission by virally inactivated clotting factor concentrates. *Transfusion*. 2012;52:1482–9. <http://dx.doi.org/10.1111/j.1537-2995.2011.03420.x>
3. Sharp CP, Lail A, Donfield S, Simmons R, Leen C, Klennerman P, et al. High frequencies of exposure to the novel human parvovirus PARV4 in hemophiliacs and injection drug users, as detected by a serological assay for PARV4 antibodies. *J Infect Dis*. 2009;200:1119–25. <http://dx.doi.org/10.1086/605646>
4. Simmonds P, Manning A, Kenneil R, Carnie FW, Bell JE. Parenteral transmission of the novel human parvovirus PARV4. *Emerg Infect Dis*. 2007;13:1386–8. <http://dx.doi.org/10.3201/eid1309.070428>
5. Sharp CP, Vermeulen M, Nebie Y, Djoko CF, LeBreton M, Tamoufe U, et al. Epidemiology of human parvovirus 4 infection in sub-Saharan Africa. *Emerg Infect Dis*. 2010;16:1605–7. <http://dx.doi.org/10.3201/eid1610.101001>
6. Lavoie M, Sharp CP, Pepin J, Pennington C, Foupouapouognigni Y, Pybus OG, et al. Human parvovirus 4 infection, Cameroon. *Emerg Infect Dis*. 2012;18:680–3. <http://dx.doi.org/10.3201/eid1804.110628>
7. Chen MY, Yang SJ, Hung CC. Placental transmission of human parvovirus 4 in newborns with hydrops, Taiwan. *Emerg Infect Dis*. 2011;17:1954–6. <http://dx.doi.org/10.3201/eid1710.101841>
8. Simmons R, Sharp C, McClure CP, Rohrbach J, Kovari H, Frangou E, et al. Parvovirus 4 infection and clinical outcome in high-risk populations. *J Infect Dis*. 2012;205:1816–20. <http://dx.doi.org/10.1093/infdis/jis291>
9. Sharp CP, LeBreton M, Kantola K, Nana A, Diffo Jle D, Djoko CF, et al. Widespread infection with homologues of human parvoviruses B19, PARV4, and human bocavirus of chimpanzees and gorillas in the wild. *J Virol*. 2010;84:10289–96. <http://dx.doi.org/10.1128/JVI.01304-10>
10. May J, Drexler JF, Reber U, Sarpong N, Adjei O, Panning M, et al. Human parvovirus 4 viremia in young children, Ghana. *Emerg Infect Dis*. 2012;18:1690–2. <http://dx.doi.org/10.3201/eid1810.111836>

Address for correspondence: Philippa C. Matthews, Peter Medawar Building, Nuffield Department of Medicine, University of Oxford, South Parks Rd, Oxford OX1 3SY, UK; email: [p.matthews@doctors.org.uk](mailto:p.matthews@doctors.org.uk)

## Co-infection with Avian (H7N9) and Pandemic (H1N1) 2009 Influenza Viruses, China

Wanju Zhang,<sup>1</sup> Dongyi Zhu,<sup>1</sup> Di Tian,<sup>1</sup> Lei Xu, Zhaokui Zhu, Zheng Teng, Jing He, Shan Shan, Yi Liu, Wei Wang, Zhenghong Yuan, Tao Ren, Yunwen Hu

Author affiliations: Shanghai Public Health Clinical Center of Fudan University, Shanghai, China. (W. Zhang, D. Tian, L. Xu, J. He, Y. Liu, W. Wang, Z. Yuan, Y. Hu); East Hospital, Tongji University School of Medicine, Shanghai (D. Zhu, S. Shan, T. Ren); Shanghai Municipal Center for Disease Control and Prevention, Shanghai (Z. Zhu, Z. Teng); Shanghai Medical College of Fudan University, Shanghai (Z. Yuan, Y. Hu)

DOI: <http://dx.doi.org/10.3201/eid2104.141560>

<sup>1</sup>These authors contributed equally to this article.